Kenyanthropus platyops, was named. The cover story on a new 3.5 million year old cranium announced it as the long-sought, flat-faced ancestor of *H. rudolfensis* [8]. Entitled "New hominin genus from eastern Africa shows diverse middle Pliocene lineages," this 2001 contribution [8] characterized early hominids as participants in "a diet-driven adaptive radiation." Its authors saw within the Turkana Basin an express line to humanity — from *K. platyops* to *H. rudolfensis*, then on through the *H. erectus* 'Turkana Boy' to modern humans; other fossils were relegated to mere side branches. However, geological distortion of the allegedly paternal cranium derailed this putative new genus: today, only very few seriously promote *Kenyanthropus* as a genus distinct from *Australopithecus*, and many consider it conspecific with *Au. afarensis* [9].

The next Kenyan hominid diversity assertion was the 2007 claim that an isolated maxilla indistinguishable from *H. erectus* [10] rather represented a contemporary, dead-end example of *H. habilis.* The evidence and arguments again proved unconvincing. Finally, the most recent paper [1] now completes an 11-year *Nature* cover trilogy promoting hominid lineage diversity in Kenya's Turkana Basin. This trilogy also underpins the popular myth that this basin was the central cauldron of human evolution, a vision most recently advertised on the PBS/NOVA/National Geographic special television program entitled "Bones of Turkana" [11].

Paleoanthropology's ecosystem of publishing, access, fundraising, career advancement, media promotion and celebrity seems squarely aligned against the field's ability to self regulate, a condition exacerbated by the limited fossil resources available [12]. There is ample and obvious motivation for authors to generate 'new' species names in this environment. Readers should, therefore, beware of attendant species diversity claims. Illegitimate names have become part and parcel of the symbiosis itself. Furthermore, 'chronospecies' are merely artificial segments of evolving species lineages, rather than truly separate species. Such assertions of biological species diversity via taxonomic hyperbole are questionable representations of the real paleobiology of our ancestors and their few close, now extinct biological relatives [13–15]. Despite the branch waving, our family tree still resembles a saguaro cactus more than a creosote bush [16].

Fossil collection teams in Africa have made laudable progress, but the early *Homo* fossil record is still in dire need of amplification. The new juvenile maxilla now constitutes slightly better evidence for *H. rudolfensis* being contemporary with, but separate from, the better-known *H. habilis.* But did either one give rise to Eurasia's primitive *H. erectus*? Is the latter an African export, or import? And what was the timing of all of these events?

More fossils will be needed to tell. Unfortunately, funding for field research is currently constrained by granting agencies diverting more and more money into peripheral activities and expensive equipment manipulated by laboratory-bound panelists and pundits [17,18]. As a consequence, the basic logistical support needed for long-term field research — from pickup trucks to fossil preparators — is woefully under-funded. Until a better balance is achieved — and better biological understanding applied — the origins of our genus will remain shrouded by a paucity of paleobiological data.

References

1. Leakey, M.G., Spoor, F., Dean, M.C., Feibel, C.S., Anton, S.C., Kiarie, C., and Leakey, L. (2012). New fossils from Koobi Fora in northern Kenya confirm taxonomic diversity in early *Homo*. Nature *488*, 201–204.
2. Wood, B. (2011). Did early *Homo* migrate "out of" or "in to" Africa? Proc. Natl. Acad. Sci. USA *108*, 10375–10376.
3. Leakey, R.E.F. (1973). Evidence for an advanced Plio-Pleistocene hominid from East Rudolf, Kenya. Nature *242*, 447–450.
4. Wood, B.A. (2012). Facing up to complexity. Nature *488*, 162–163.
5. Gould, S.J. (1976). Ladders, bushes, and human evolution. Nat. Hist. Mag. *85*, 24–31.
6. Berger, L.R. (2012). *Australopithecus sediba* and the earliest origins of the genus *Homo*. J. Anthropol. Sci. *90*, 1–16.
7. Lordkipanidze, D., Vekua, A., Ferring, R., Rightmire, G.P., Zollikofer, C.P.E., *et al*. (2006). A fourth hominin skull from Dmanisi, Georgia. Anat. Rec. A *288A*, 1146–1157.
8. Leakey, M.G., Spoor, F., Brown, F.H., Gathogo, P.N., Kiarie, C., Leakey, L.N., and McDougall, I. (2001). New hominin genus from eastern Africa shows diverse middle Pliocene lineages. Nature *410*, 433–440.
9. White, T.D. (2003). Early hominids—diversity of distortion? Science *299*, 1994–1996.
10. Spoor, F., Leakey, M.G., Gathogo, P.N., Brown, F.H., Anton, S.C., McDougall, I., Kiarie, C., Manthi, F.K., and Leakey, L.N. (2007). Implications of new early *Homo* fossils from Ileret, east of Lake Turkana, Kenya. Nature *448*, 688–691.
11. Heminway, J. (producer) (2012). Bones of Turkana. PBS/NOVA/National Geographic Television. http://www.pbs.org/programs/bones-turkana/.
12. White, T.D. (2004). Managing paleoanthropology's nonrenewable resources: a view from afar. Comp. Rend. Palevol *3*, 341–351.
13. White, T.D. (2010). Human evolution: how has Darwin done? In Evolution Since Darwin: The First 150 Years, M.A. Bell, D.J. Futuyma, W.F. Eanes, and J.S. Levinton, eds. (Sunderland, MA: Sinauer), pp. 519–560.
14. White, T.D. (2009). Human origins and evolution: Cold Spring Harbor, déjà vu. Cold Spr. Harbor Symp. Quant. Biol. *74*, 335–344.
15. White, T.D. (2009). Ladders, bushes, punctuations, and clades: Hominid paleobiology in the late Twentieth Century. In The Paleobiological Revolution: Essays on the Growth of Modern Paleontology, D. Sepkoski and M. Ruse, eds. (Chicago: University of Chicago Press), pp. 122–148.
16. White, T.D. (2011). Bones, stones, and genes: The origin of modern humans; Lecture 4 – Hominid Paleobiology. 2011 Holiday Lectures, Howard Hughes Medical Institute. http://www.hhmi.org/biointeractive/lectures/index.html.
17. White, T.D. (2000). A view on the science: Physical anthropology at the Millennium. Am. J. Phys. Anthrop. *113*, 287–292.
18. White, T.D. (2010). Q & A. Curr. Biol. *20*, R6–R8.

Human Evolution Research Center (HERC) and Department of Integrative Biology, 3101 Valley Life Sciences Building, UC Berkeley, Berkeley, CA 94720, USA.
E-mail: timwhite@berkeley.edu

http://dx.doi.org/10.1016/j.cub.2012.12.001

DNA Repair: Trust but Verify

Damage recognition is a key initial step in DNA repair. A recent study puts to rest the debate of whether XPD helicase 'verifies' the appropriateness of the DNA damage to be mended by the nucleotide excision repair machinery.

Maria Spies

Nucleotide excision repair (NER) recognizes and repairs a broad repertoire of genotoxic DNA lesions. In mammalian cells, it constitutes a major mechanism for the removal of diverse types of DNA damage ranging from pyrimidine–pyrimidine intra-strand cross links induced by UV light to bulky

DNA adducts formed by environmental carcinogens, reactive oxygen species and cellular metabolites [1,2]. The versatile nature of NER allows it to excise and fully repair lesions whose only common features are dsDNA helix distortion and chemical modification of the DNA bases. Over 30 distinct proteins carry out NER in human cells. Their precise roles, modes of action, and how they are integrated into the complex molecular circuitry of the cell are still not fully unmasked. The major steps in the NER, however, are beginning to fall into place.

The prerequisite of a successful DNA repair event is the ability of a designated molecular machinery to recognize the repairable damage among native DNA and lesions destined for other repair mechanisms.

NER is initiated via two distinct mechanisms: in transcription-coupled repair (TCR), the presence of the damage within the actively transcribed DNA strand stalls RNA polymerase II [3]; damage elsewhere in the genome is identified by the global genome repair (GGR) pathway, which uses UV–DDB and XPC–Rad23 complexes to identify the NER compatible lesions. UV–DDB recognizes the chemistry of modified bases and destabilizes the duplex [4]. XPC is the most important initial responder in GGR. It recognizes a single-stranded character of non-hydrogen bonded bases opposing the lesion sites [5]. It may act by itself or in conjunction with UV–DDB.

The diversity of DNA lesions repaired by NER and multiple damage recognition mechanisms necessitate a bipartite damage recognition and verification process. First, the damage is recognized due to its ability to stall RNA polymerase or because it destabilizes the Watson-Crick double helix and facilitates flipping out of the two base pairs. Having distinct origins, both GGR and TCR lead to assembly of the same basic NER machinery. This machinery verifies whether a particular stalled RNA polymerase or DNA-associated XPC signifies a cognate damage. Both sub-pathways recruit transcription factor IIH (TFIIH), which generates a partially unwound intermediate and signals to the downstream NER proteins (XPA, RPA, XPF–ERCC1 and XPG) to proceed with the excision [6,7]. The verification process is postulated to involve formation of a stable signaling complex that persists at or near the damage long enough to recruit the downstream machinery. The likely candidates to carry out damage verification include TFIIH [7,8] and replication protein A (RPA), a single-stranded DNA binding protein which stabilizes the DNA bubble generated by TFIIH [9]. In this issue of *Current Biology*, Mathieu and colleagues [10] demonstrate that a superfamily II (SF2) DNA XPD helicase, one of the TFIIH subunits, plays an important role in damage verification and demarcation of the lesion site [11]. The authors build on their previous observation that archaeal XPD from *Ferroplasma acidarmanus* (*Fa*XPD) is stalled by a cyclobutane pyrimidine dimer (CPD), a bulky photoproduct repaired by NER [12]. This observation spanned a controversy: not every archaeal XPD seems to be affected by the presence of a CPD. Work by Rudolf and colleagues published at about the same time demonstrated that *Sulfolobus acidocaldarius* XPD unwound CPD-containing DNA as well as it did undamaged duplex, or substrates containing abasic sites or extrahelical fluorescein adducts [13]. In contrast, CPD in a related *Sulfolobus* species is recognized by a single-stranded DNA binding protein SSB, which was proposed to attract the NER proteins to the lesion site [14]. Since both studies involved archaeal XPD homologues and the archaeal DNA repair pathways are still not fully defined, one could not help but ask: which of the two enzymes accurately represents activity of human XPD? This question was resolved in the present study [11]. Based on recent structural and biochemical data [15,16], Mathieu and colleagues predicted that the damage verification locus may reside within an extended DNA-binding site on the back of XPD helicase. Rationally designed mutants Y192A, R196A and R196E (in human XPD nomenclature) did indeed show a separation of functions. In cellular assays, the XPD^{Y192A}- and XPD^{R196E}-containing complexes associated with the UV-induced lesions less efficiently and were more dynamic as revealed by fluorescence recovery after photobleaching (FRAP) measurements. The mutations caused reduced CPD excision and generally defective NER. Notably, the two mutations had no detectable effect on XPD function in transcription. Analogous mutants of *Fa*XPD displayed helicase activity similar to that of the wild-type protein, but, in contrast to wild-type XPD, were not stalled by the presence of CPD, confirming that Y192 and R196 do indeed belong to the damage sensor site, which allows XPD helicase to verify the NER repairable damage and initiate its demarcation and excision. Interestingly, the size and the shape of the groove which features Y192 and R196 vary between published structures of archaeal XPD helicases [17–20]. These differences were suggested to signify distinct conformations of XPD and to reflect the unique mechanism whereby XPD helicase couples directional translocation to gripping and releasing ssDNA [20]. In light of the Mathieu *et al.* study, these differences may also set apart XPD homologues that do and do not act as the damage sensors. Indeed, R196 is not conserved in *S. acidocaldarius* XPD, which has N144 in the corresponding location and is not stalled by CPD. *Thermoplasma acidophilum* XPD, whose structures feature a tighter central pore opening [15,19], was not tested for its ability to recognize CPD, but K170A substitution in this helicase (analog of R196A) moderately enhances helicase activity [15,16].

The proposed damage verification mechanism positions TFIIH to act as a central hub in NER where TCR and GGR channel the suspected lesions to be rejected or handed off for excision (Figure 1). The reported finding, however, does not negate the possibility that the damage verification mechanism has additional layers and involves the downstream players including RPA as well.

The work by Mathieu and colleagues [11] made a significant breakthrough in our understanding of the key steps in NER. However, it left a number of enigmas. The authors, for example, observed that the ectopic expression of human XPD in rodent cells compensates for the deficiency in UV–DDB2, which otherwise results in slow CPD removal. It will be interesting to learn whether this compensation requires XPD to act outside TFIIH.

To date, structural information as well as information on the dynamics

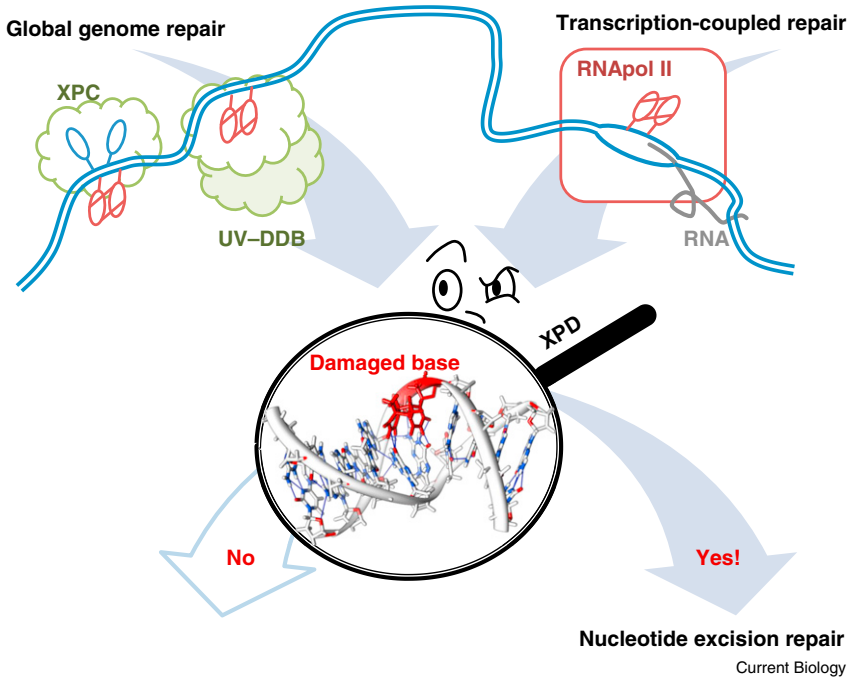

Figure 1. Nucleotide excision repair.

UV lesions, exemplified here by the cyclobutane pyrimidine dimer (CPD) depicted in red within the dsDNA structure (inset) and in the schematic representation of the DNA, are initially recognized by the global genome repair (GGR) or transcription-coupled repair (TCR) machineries. The first responders in GGR, XPC and UV–DDB dimer are shown in green. RNA polymerase stalled at the CPD at the recognition step of TCR is shown in red. XPD helicase serves as a damage sensor both in GGR and TCR sub-pathways of nucleotide excision repair.

of XPD is limited. Full understanding of lesion verification and in particular the molecular determinants of this process can be greatly facilitated by structures of XPD bound to damaged and native DNA.

Finally, the conservation of the FeS and ARCH auxiliary domains in the helicases related to XPD may suggest similar recognition mechanisms employed by these FeS-containing helicases. XPD paralogues FACNJ, RTEL1 and CHLR1 recognize various non-standard structures: branched DNA, D-loops, and G-quadruplexes among many. Similar to XPD, these are multifunctional enzymes that act as DNA translocases, DNA helicases and as hubs for assembly or different DNA repair and maintenance machineries. It is foreseeable that these helicases employ a sensing mechanism similar to that of XPD. When targeted to the DNA substrate via protein–protein interactions the helicase may need to use its translocation or helicase activity; dimerization, protein partners or activation/inactivation by posttranslational modifications may provide the means of switching between these activities. The choice between motor activity and signaling role, on the other hand, may be triggered when these helicases stall at the damage or an unconventional DNA structure. The work by Naegeli's group presents a beautiful example of how structural information can inspire a functional study of the helicase, which reveals its unconventional role in a fundamental cellular process.

References

1. Kuper, J., and Kisker, C. (2012). Damage recognition in nucleotide excision DNA repair. Curr. Opin. Struct. Biol. *22*, 88–93.
2. Gillet, L.C., and Scharer, O.D. (2006). Molecular mechanisms of mammalian global genome nucleotide excision repair. Chem. Rev. *106*, 253–276.
3. Hanawalt, P.C. (1994). Transcription-coupled repair and human disease. Science *266*, 1957–1958.
4. Scrima, A., Koníčková, R., Czyzewski, B.K., Kawasaki, Y., Jeffrey, P.D., Groisman, R., Nakatani, Y., Iwai, S., Pavletich, N.P., and Thomä, N.H. (2008). Structural basis of UV DNA-damage recognition by the DDB1–DDB2 complex. Cell *135*, 1213–1223.
5. Min, J.H., and Pavletich, N.P. (2007). Recognition of DNA damage by the Rad4 nucleotide excision repair protein. Nature *449*, 570–575.
6. Volker, M., Mone, M.J., Karmakar, P., van Hoffen, A., Schul, W., Vermeulen, W., Hoeijmakers, J.H., van Driel, R., van Zeeland, A.A., and Mullenders, L.H. (2001). Sequential assembly of the nucleotide excision repair factors in vivo. Mol. Cell *8*, 213–224.
7. Coin, F., Oksenych, V., Mocquet, V., Groh, S., Blattner, C., and Egly, J.M. (2008). Nucleotide excision repair driven by the dissociation of CAK from TFIIH. Mol. Cell *31*, 9–20.
8. Sugasawa, K., Akagi, J., Nishi, R., Iwai, S., and Hanaoka, F. (2009). Two-step recognition of DNA damage for mammalian nucleotide excision repair: Directional binding of the XPC complex and DNA strand scanning. Mol. Cell *36*, 642–653.
9. He, Z., Henricksen, L.A., Wold, M.S., and Ingles, C.J. (1995). RPA involvement in the damage-recognition and incision steps of nucleotide excision repair. Nature *374*, 566–569.
10. Beyer, D.C., Ghoneim, M.K., and Spies, M. (2013). Structure and mechanisms of SF2 DNA helicases. Adv. Exp. Med. Biol. *767*, 47–73.
11. Mathieu, N., Kaczmarek, N., Ruthemann, P., Luch, P., and Naegeli, H. (2013). DNA quality control by a lesion sensor pocket of the xeroderma pigmentosum group D helicase subunit of TFIIH. Curr. Biol. *23*, 204–212.
12. Mathieu, N., Kaczmarek, N., and Naegeli, H. (2010). Strand- and site-specific DNA lesion demarcation by the xeroderma pigmentosum group D helicase. Proc. Natl. Acad. Sci. USA *107*, 17545–17550.
13. Rudolf, J., Rouillon, C., Schwarz-Linek, U., and White, M.F. (2010). The helicase XPD unwinds bubble structures and is not stalled by DNA lesions removed by the nucleotide excision repair pathway. Nucleic Acids Res. *38*, 931–941.
14. Cubeddu, L., and White, M.F. (2005). DNA damage detection by an archaeal single-stranded DNA-binding protein. J. Mol. Biol. *353*, 507–516.
15. Kuper, J., Wolski, S.C., Michels, G., and Kisker, C. (2012). Functional and structural studies of the nucleotide excision repair helicase XPD suggest a polarity for DNA translocation. EMBO J. *31*, 494–502.
16. Pugh, R.A., Wu, C.G., and Spies, M. (2012). Regulation of translocation polarity by helicase domain 1 in SF2B helicases. EMBO J. *31*, 503–514.
17. Fan, L., Fuss, J.O., Cheng, Q.J., Arvai, A.S., Hammel, M., Roberts, V.A., Cooper, P.K., and Tainer, J.A. (2008). XPD helicase structures and activities: Insights into the cancer and aging phenotypes from XPD mutations. Cell *133*, 789–800.
18. Liu, H., Rudolf, J., Johnson, K.A., McMahon, S.A., Oke, M., Carter, L., McRobbie, A.M., Brown, S.E., Naismith, J.H., and White, M.F. (2008). Structure of the DNA repair helicase XPD. Cell *133*, 801–812.
19. Wolski, S.C., Kuper, J., Hanzelmann, P., Truglio, J.J., Croteau, D.L., Van Houten, B., and Kisker, C. (2008). Crystal structure of the FeS cluster-containing nucleotide excision repair helicase XPD. PLoS Biol. *6*, 1332–1342.
20. Wolski, S.C., Kuper, J., and Kisker, C. (2010). The XPD helicase: XPanDing archaeal XPD structures to get a grip on human DNA repair. Biol. Chem. *391*, 761–765.

Department of Biochemistry, University of Iowa Carver College of Medicine, IA 52242, USA.
E-mail: maria-spies@uiowa.edu

http://dx.doi.org/10.1016/j.cub.2012.12.019